Remarks and Arguments

Claims 4-24 are pending in this application. Claims 1-3 have been cancelled. Claims 4-22 have been amended. New claims 23 asnd 24 have been added. No new matter has been added.

The present amendments

The present amendments have been made to facilitate prosecution of this application, and not in response to any rejection. In view of the cancellation of claims 1-3, claim 4 is now the head claim relating to the conjugates of the invention. The definitions of the groups CT, AA1, AA2, AA3, AA4, Sp', and Sp in original claim 4 have been replaced with those from original claim 5, and therefore have been deleted from claims 5, 9, and 13, as no longer needed.

The terms "alkine" and "methine" have been deleted in several locations as superfluous. In German, there are terms such as "alkin" and "methin", which indicate a three-fold substituted carbon atom. "Alkine" would correspond to a substituted alkylene group, and "methine" would correspond to a methylene group. Note, however, that the term "alkin" is not to be confused with "alkinyl", which is the German spelling for "alkynyl".

Restriction requirement

In response to the restriction requirement, applicants elect to proceed with prosecution of restriction group I, now relating to claims 4-18, drawn to molecular conjugates.

Applicants do not understand the examiner's further requirement to elect a "patentably distinct sequence of the conjugate". If the examiner means to require election of a single conjugate, applicants elect the conjugate of example 3.13 on page 185 of the specification. If the examiner means to require election of the amino acid sequence portion of the elected conjugate, applicants elect the dipeptide sequence of conjugate example 3.13, namely, his-val (both L enantiomers).

The nature of the present invention

The examiner seems to think that the claimed conjugates are polypeptides. He is mistaken. This invention broadly relates to molecular conjugates in which an integrin antagonist is connected to a cleavable linking unit, which is in turn connected to a cytostatic material such as camptothecin. The cleavable linking unit can be one to four amino acid residues, or a cleavable spacer which is not an amino acid residue or peptide, or it can be one to four amino acid residues linked to a cleavable spacer.

The exemplified conjugates demonstrate that the one to four amino acid residues which, alone or together with the spacer, connect the integrin antagonist portion of the conjugate to the cytostatic portion of the conjugate, represent only a small portion of the molecular conjugates being claimed.

The conjugates of the invention are claimed in Markush terminology, in the same way most organic compounds are claimed. The only real difference between the type of claims employed herein and the type of claims employed in more usual applications dealing with organic compounds is that in the present application, we are dealing with large complex molecular entities, while the more usual applications deal with smaller and less complex molecules.

In establishing his restriction requirement, the examiner has not followed MPEP §803.02, which provides directions for examining Markush claims. Instead, he appears to be focusing only on the polypeptide linking units of the claimed conjugates, and treating the claims as if they were claims to polypeptides. This is a serious error which, if persisted in, will only cause great difficulties in the prosecution of this case.

It should be relatively easy to conduct computer searching for art relating to the claimed conjugates. One only has to search for the integrin antagonists (by structure), and for the cytostatic material (camptothecin, by structure), and also possibly (but not necessarily), for short polypeptides. The results of these substructure searches are then "anded" together to yield a set of records which include each kind of molecular segment. The number of "hits" from such searching is expected to be quite small.

The examiner is requested to deal with this application in accordance with the MPEP directions relating to Markush claims to organic compounds, and not to try to force-fit these claims into any sort of polypeptide examination protocol.

Unity of invention, and anticipation

The examiner has established four restruction groups: (I) claims 1-18, drawn to a conjugate; (II) claims 19-20, drawn to a method of making the conjugate; (III) claim 21, drawn to a pharmaceutical composition; and (IV) claim 22, drawn to a method of treatment. The examiner states that the inventions listed as groups (I) to (IV) do not relate to a single general inventive concept ..... because ..... "they lack the same or corresponding technical features for the following reasons: the conjugate of group I lacks novelty (I.e., it is anticipated by prior art reference)- see e.g., J. Clin. Invest., vol. 96, pp 1815-1822, 1995."

Applicants maintain that the claims of the four restriction groups do relate to a single inventive concept because they all relate somehow to the conjugates of the invention. Even if the examiner were correct in his assertion that the claimed conjugates are anticipated (which the applicants do not accept), this should not negate unity of invention. Rather, it should simply mean that the claims to the conjugates (and possibly all the claims) would be unpatentable.

Turning now to the examiner's assertion that "the conjugate of group (I) lacks novelty", the applicants respond as follows. First, restriction group (I) included claims 1-18, which range from broad and functional, to narrower with substantial structural specificity. There is no single "conjugate of group (I)", and it is exceedingly unlikely that any single reference could anticipate all of the claims 1-18. Secondly, the article cited by the examiner is not deemed to anticipate any of the claims of this application. The reference states "In this report we provide evidence that integrin $\alpha_v\beta_3$ is highly expressed on angiogenic vessels associated with biopsies of malignant human breast carcinoma, suggesting that integrin $\alpha_v\beta_3$ may be a useful marker of blood vessels associated with human breast cancer tissue. Furthermore, systemic administration of mAb LM609 directed to integrin $\alpha_v\beta_3$ not only disrupts human angiogenesis but reduces the growth and invasive properties of human breast carcinoma in the SCKS mouse/human chimeric model. Therefore, antagonists of integrin $\alpha_v\beta_3$ may provide a novel approach for the treatment of

malignant breast tumors." The reference employs monoclonal antibodies as $\alpha_v\beta_3$ antagonists, but does not disclose any molecular conjugates, and so cannot anticipate the present conjugate claims.

Amendment to the specification

The amendment to the chemical structure of the conjugate of example 3.13 is to correct the indicated configuration of the valyl residue which is adjacent to the camptothecin moiety. The original structure showed this valyl residue as D-valyl, but this is incorrect, as shown by the fact that L-valyl is employed in the starting material 1.3, and all the other examples of conjugates prepared using starting material 1.3 are correctly drawn to indicate the L-valyl group stereochemistry.

Respectfully submitted,

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